Adjuvant Surgery after Carboplatin and VP16 in Resectable Small Cell Lung Cancer

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Introduction: The real benefit of surgical treatment of small cell lung cancer (SCLC) has never been demonstrated, mainly because of the rarity of surgical cases and the difficulty in comparing surgical and medical series for the different classifications systems used by surgeons (tumor, node, metastasis) and medical oncologists and radiotherapists (Veterans Administrations Lung Cancer Study Group).

Materials and Methods: We prospectively assessed the utility of surgery after chemotherapy (carboplatin plus VP16 with or without ifosfamide) with or without radiotherapy in 23 patients with preoperative diagnosis of resectable stage I to IIIA SCLC. A median of three (range: three to six) courses of chemotherapy were administered. Five pneumonectomies, 12 lobectomies (seven sleeve resections), and two segmentectomies were performed, and all except one received radical lymph node dissection. Four (17%) patients received exploratory thoracotomy. Nine (39%) patients received postoperative thoracic radiotherapy.

Results: Pathological stages were complete response in four patients, stage I in seven patients, stage II in seven patients, and stage III in five patients. Thirty-day morbidity and mortality were 9% and 0%, respectively. Surgery-related mortality at 90 days was 9%. Median follow-up was 19 months. Overall and local relapse rates were 52% and 17%, respectively. Median overall and disease-free survival were 24 and 12 months. Patients with complete response or pathological stage I had a significantly better Kaplan–Meier survival and lower incidence of relapse than those with more advanced pathological stage ($p = 0.025$ and 0.027, respectively, log rank).

Conclusions: Survival after chemotherapy and surgery in the series correlated with pathological but not pretreatment stage. Only patients with pathological stage 0 or I disease seem to benefit from surgical resection.

Key Words: Small cell lung cancer, Surgery, Chemotherapy, Induction treatment.

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The randomized Medical Research Council (MRC) study published in 1973 found that radiotherapy alone was superior to radiotherapy plus surgery for limited small cell lung cancer (SCLC).[1] The MRC findings were supported by Osterlind et al's[2] large retrospective study published in 1985. Furthermore, the Lung Cancer Study Group randomized trial, published in 1994, which compared radiotherapy with radiotherapy plus surgery for the local treatment of SCLC after chemotherapy, also found that surgery did not improve median or long-term survival.[3] Nevertheless, some of these studies had limitations. In the MRC study, only 48% of the surgical arm received radical resection, and 18% received exploratory thoracotomy only (the main diagnostic procedure at the time). Similarly, in the Osterlind et al.[2] study, only 33% of patients received radical resection, and 10% were found to be metastatic on postsurgery investigations.

Other studies, by contrast, have found surgical resection after chemotherapy useful in early-stage SCLC, particularly in stage I or II disease.[4–9] Nevertheless, most of these studies were retrospective and used various treatment combinations and patient-selection criteria. Thus, the role of surgery, in addition to chemotherapy, in achieving local control and in increasing survival in SCLC has not been established.

We performed a single-center prospective study to provide indications as to the utility of surgical resection after chemotherapy, with or without thoracic irradiation, in patients with resectable stage I to IIIA SCLC. We assessed survival, recurrences, treatment-related morbidity and mortality, and, in more recent patients, the role of positron emission tomography (PET) in preoperative staging.

MATERIALS AND METHODS

Between 1998 and 2004, all patients presenting at our Thoracic Surgery Division with histologically or cytologically documented stage I to IIIA resectable SCLC, age over 18 years, Eastern Cooperative Oncology Group performance status of 0 to 2, and a predicted postoperative forced expiratory volume in 1 second above 40% on spirometry were included in a prospective study employing surgery after systemic chemotherapy, with postoperative radiotherapy in selected cases.

Preoperative staging included whole-body computed tomography (CT) and bronchoscopy, with brain magnetic

resonance imaging and abdominal ultrasonography in cases of suspected lesion at the brain or liver level. Mediastinoscopy or mediastiotomy was usually performed in patients with mediastinal lymph nodes >1 cm on CT. PET was performed for restaging after chemotherapy in recent cases. At least three courses of carboplatin/cisplatin and VP16, with or without ifosfamide, were administered to all patients. Radical surgery included systematic lymph node dissection according to the current International Association for the Study of Lung Cancer guidelines.[10] The procedure included the removal of at least three hilar and interlobar nodes and three mediastinal nodes from three stations, in which the subcarinal was always included. Postoperative thoracic radiotherapy was usually given to patients with pathologic mediastinal nodes after radical surgery, or unresectable or partially resected disease.

Survival times, assessed from the day of surgery until death or most recent follow-up, were estimated by the Kaplan–Meier method and were compared by the log-rank test.

RESULTS

Twenty-three consecutive patients (nine [39%] women; median age, 64 years [range: 38–81] were enrolled. Clinical stage before treatment was I in nine (39%) patients, II in five patients (22%), and IIIA in nine patients (39%). Eight patients had clinical mediastinal involvement at chest CT, and three of them underwent pathological confirmation of N2 disease (two mediastinoscopy and one mediastinotomy). All patients received a systemic treatment consisting of cisplatin/carboplatin associated with etoposide. Ifosfamide was also combined in seven patients. In detail, 13 patients received 360 mg/m^2 of etoposide plus carboplatin area under the curve of 5,[11] and three patients received 360 mg/m^2 of etoposide plus 80 mg/m^2 of cisplatin. Seven patients received 300 mg/m^{2}of carboplatin, 5 g/m^2 of ifosfamide, and 360 mg/m^2 of etoposide. The median number of cycles was four (range: three to six).

Clinical response to chemotherapy was assessable in 22 patients according to the Response Evaluation Criteria in Solid Tumors.[12] Nineteen (83%) patients responded. Among them, five were complete responses (22%), 14 were partial responses (64%), two had a stable disease (9%), and one patient had tumor progression (5%). None of the patients interrupted chemotherapy because of toxicity.

Nineteen (83%) patients underwent surgery with curative intent: pneumonectomy in five (22%), sleeve lobectomy in eight (35%), lobectomy in four (17%), and segmentectomy in two (8%); all but one of these received systematic lymph node dissection. The remaining four (17%) patients received exploratory thoracotomy only: one because of vertebral invasion, two because of extensive mediastinal node involvement, and one because of limited functional reserve in light of the requirement for pneumonectomy.

Pathological stage was 0 (complete response to chemotherapy) in four patients (17% of total); I in seven patients (30%), II in seven patients (30%), and III in five patients (22%). Mixed histology (SCLC and NSCLC) was found in two patients (9%). Table 1 reports the correspondence between clinical pretreatment stage and pathological stage.

TABLE 1. Clinical Tumor, Node, Metastasis Staging Related to the Final Pathological Finding

	cIA	cIB	cIIA	cIIB	cIIIA	Total
0	1	—	—	1	2	4
pIA	1	4	—	—	1	6
pIB	—	1	—	—	1	2
pIIA	1	—	—	2	1	4
pIIB	—	—	—	1	1	2
pIIIA	—	1	—	—	3	4
pIIIB	—	—	—	1	—	1
Total	3	6	—	5	9	23

Nine patients were preoperatively staged as IIIA, but six of them (67%) were downstaged after surgery. p, pathological staging; c, clinical staging.

Median postoperative hospitalization was 6.5 days. Postoperative complications occurred in two (8.7%) patients and included one hemothorax and one episode of cardiac ischemia. Thirty-day mortality was 0%. Two (8.7%) patients had fatal late complications: bronchovascular fistula with hemorrhage into the airway 56 days after sleeve lobectomy, and pulmonary embolism associated with pneumonia 3 months after right pneumonectomy.

Postoperative thoracic radiotherapy was given to nine patients. Indications were exploratory thoracotomy in four patients, mediastinal nodal metastasis in three, and hylar nodal metastasis in two. Fields of irradiation included mediastinum and lung in four cases (exploratory thoracotomy; mean doses: 60 Gy on lung and 50 Gy on mediastinum). Four subjects received irradiation of mediastinum only (54 Gy), one of them associated with subclavicular regions. Another patient received prophylactic cranial irradiation (26 Gy) and additional postoperative chemotherapy.

Median follow-up after surgery was 20 months.

Overall 2- and 3-year survival were 49% (95% CI, 22%–76%) and 25% (95% CI, 0%–61%), respectively. Median overall survival was 24 months (Figure 1) and correlated with pathological stage ($p = 0.025$ log rank) but not with pretreatment clinical stage ($p = 0.6$).

According to clinical stage, 2-year survival was 91% (95 CI, 74%–100%) for stage 0 and I disease, and it was 14% (95 CI, 0%–40%) for stage II and III disease ($p = 0.025$) (Figure 2).

Twelve (52%) patients relapsed, and four of them (17%) had local recurrence. The brain was the most frequent (39%) site of distant metastases.

The recurrence rate correlated significantly with pathological stage: 18% in stage 0 and I disease; 71% in stage II, and 100% in stage IIIA ($p = 0.046$).

Median disease-free survival was 12 months (Figure 3), and cumulative incidence of relapse was correlated with pathological stage (stage 0 and I versus stage II and III; $p = 0.027$) (Figure 4).

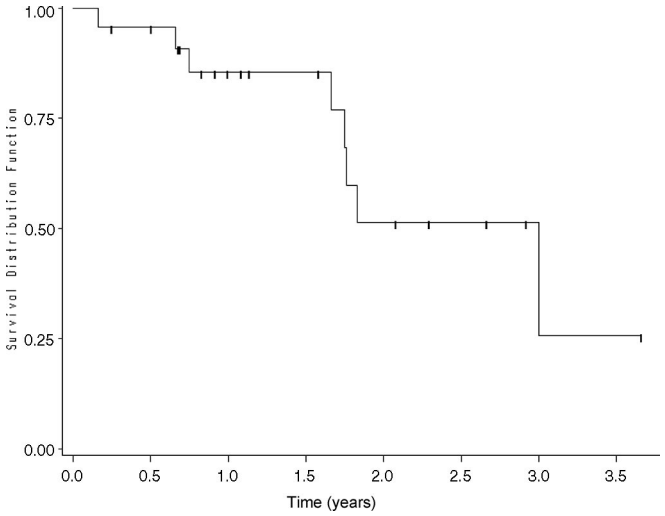

FIGURE 1. Overall (Kaplan–Meier) survival in 23 SCLC patients.

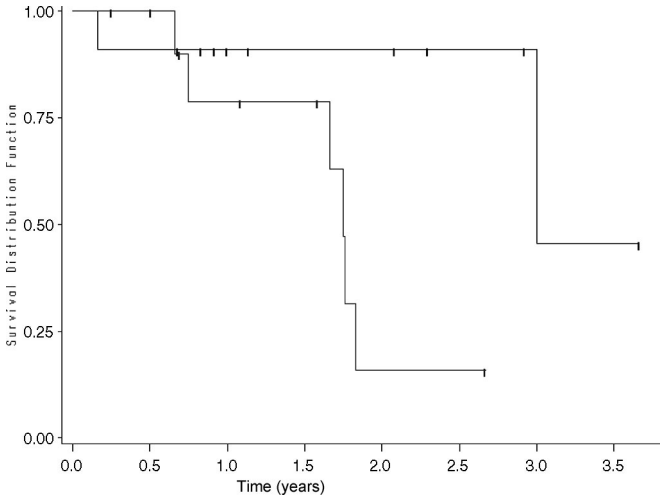

FIGURE 2. Kaplan–Meier survival according to pathological stage in 23 SCLC patients. Stage 0 and I patients had significantly better ($p = 0.025$ log-rank test) survival than stage II and III patients.

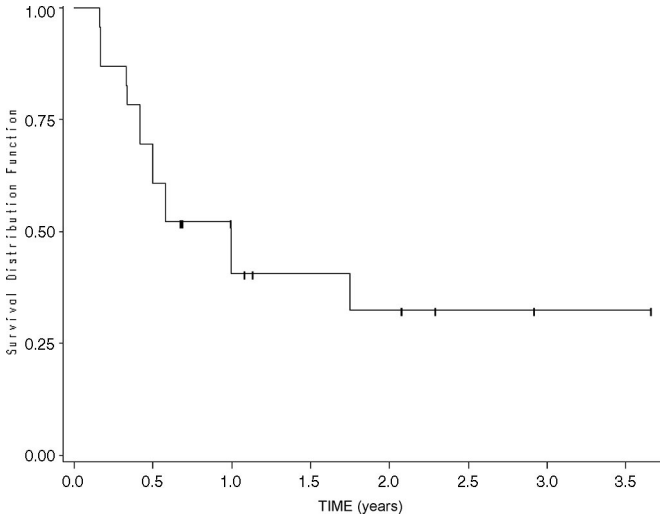

FIGURE 3. Disease-free survival curve in 23 patients with SCLC.

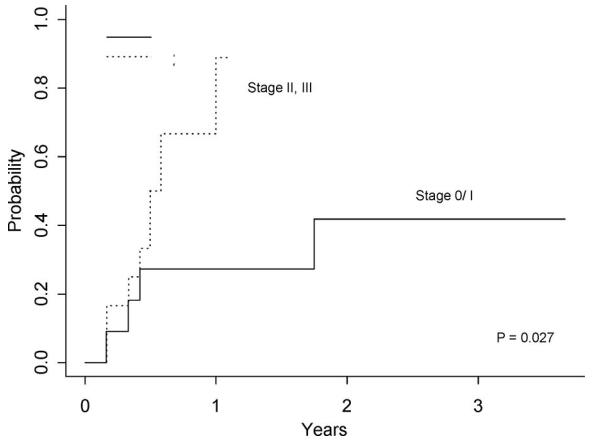

FIGURE 4. Cumulative probability of relapse according to pathological stage in 23 patients with SCLC. Patients with pathological stage 0 or I had a significantly lower relapse rate than those at stage II or III.

DISCUSSION

Theoretical advantages of surgery as part of a multimodality approach to limited SCLC are that such an approach (a) reduces local relapse rate, (b) provides immediate complete response, (c) has no effect on bone marrow, and (d) provides accurate tumor, node, metastasis staging.[13] Furthermore, mixed histology is found in 7% to 20% of resected SCLC after chemotherapy[3,6,7,14]; often, initial misdiagnosis may occur, and potentially curable cases may remain untreated (more frequently typical or atypical carcinoids, or large cell neuroendocrine tumor).

Despite these theoretical advantages, the real benefit of surgical treatment has never been demonstrated, mainly because of the difficulty of performing randomized trials, the rarity of surgical cases, and the difficulty of comparing surgical and medical series for the different classifications systems used by surgeons (tumor, node, metastasis) and medical oncologists and radiotherapists (Veterans Administrations Lung Cancer Study Group). Retrospective surgical series generally suggest that patients with stage I disease benefit when surgery is added to induction or adjuvant chemotherapy, but for clinical stage II and III disease, most retrospective studies indicate that surgery provides no benefit, although there are exceptions.[4,5,9,15] Nevertheless, most surgical series have used disparate treatment regimes and surgical resection criteria, and many have also had excessively long referral periods.[2,4,7,9,11,16]

By contrast, the patients in the present series were recruited prospectively during the last 5 years, staged with modern procedures, and submitted to the same chemotherapy regimen and type of surgical resection: therein lies the main interest of our study. We were able to perform radical surgery in most patients with acceptable morbidity and no 30-day

mortality. Nevertheless, we found that patients who responded to chemotherapy were generally demanding surgical cases because of the absence of anatomic planes and the presence of major inflammation in tissues around hylar structures. Furthermore, demanding parenchyma-sparing resections, combined with bronchial and vascular reconstruction, had to be employed in eight (35%) cases to avoid pneumonectomy. Pneumonectomy was performed in only five (22%) cases, a similar proportion to previous surgical series.[7,16]

Although overall survival was poor (25% at 3 years), outcomes in the 11 patients with pathological stage 0 or I were significantly better than those with stage II or III disease (90% versus 20% at 2 years; $p = 0.025$). Stage 0 and I patients also had a significantly ($p = 0.027$) lower cumulative relapse rate than those at stages II and III. Of the nine patients at clinical stage IIIA, six were downstaged after surgery (67%) (two had complete responses, two had stage I, and two had stage II disease), but it is important to note that only one of them was free of disease at the time this article was written (this patient had a complete response at surgery and received postoperative prophylactic cranial irradiation).

These findings are similar to those of most other studies[4,9,12,16] and suggest that it is worthwhile to offer surgery to patients with early clinical N0 disease or to those with more advanced disease downstaged to pN0 after induction chemotherapy. Patients with persistent N1 or N2 disease have poor prognosis (70%–100% recurrence rate), even after multimodality treatment.

We found that the brain was the site of most metastases, suggesting that prophylactic brain irradiation should be given to all responders. We also found that surgery provided good local disease control in that only 17% of patients developed a local recurrence. Nevertheless, similar local recurrence rates have been obtained by recent chemoradiation trials.[15,17]

Our finding that survival correlated with pathological stage after induction but not with clinical stage before induction suggests that patients with N2 disease who respond to chemotherapy to become N0 may have a greater chance of being cured than patients with N1 disease who do not respond to induction chemotherapy. Because lymph node status is the main predictor of survival,[3,4,9,14,16,18] future study on the role of PET scan for the selection of surgical candidates after induction treatment[19] would be worthwhile.

We conclude that patients with stage I SCLC or complete nodal response after chemotherapy may benefit from surgical resection. Those with persistent hylar or mediastinal node involvement after chemotherapy have a poor prognosis and are not recommended for surgery.

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